# Method and Device for Intravascular Plasma Fluid Removal

Cross-Reference to Related Applications

This is a non-provisional application based on and claiming the benefit of the filing date of provisional application ser. no. 60/247,238; filed November 13, 2000.

Statement Regarding Federally Sponsored Research or Development

"Not Applicable"

Reference to a Microfiche Appendix

"Not Applicable"

Background of the Invention:

1. Field of the Invention

This invention relates to methods for the removal of plasma fluid from a patient in need thereof, including those in what may be called a disease state, for example, congestive heart failure or moderate renal insufficiency, both of which are typically characterized by fluid overload. The invention also relates to intravascular devices for effecting the plasma fluid removal.

2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98

There are a number of techniques described in the art for removing plasma

fluid from a patient. Many patients treated using some of the more conservative of these

techniques, such as high dose diuretics or cardiac inotropes fail to adequately respond. In

such cases, the use of more invasive, risky, expensive, and/or labor-intensive therapies,

such as intermittent hemodialysis or continuous veno-venous hemodialysis or

hemofiltration are indicated.  While these extracorporeal techniques are traditionally

utilized to treat kidney failure, in the presence of fluid overload they can instead result in

the removal of bulk fluids by the use of hydraulically, or pump-driven ultrafiltration

across a dialyzer (i.e. "an artificial kidney").  It is the extracorporeal processing of blood

in these prior art techniques that makes them less than optimal for the desired purposes.


The U.S. patent literature includes a number of prior patents, which, for

the sake of easy understanding have been divided into four categories. The first category

10  is one dealing with so-called "probes."  These patents; Nos. 5,706,806, 5,607,390,

5,735,832 and 5,106,365, generally disclose devices having sealed ends and which allow

fluid to flow to the end of the probe and then back.  These devices are made for insertion

into body tissues or fluids and are used for diagnostic, not treatment purposes.  When

using these devices, the analyte of interest diffuses into the probe and then out to an

15  instrument, typically, a measuring instrument.  These devices allow monitoring of a

patient's pH, oxygen, sodium, potassium, etc. levels in the tissue of interest (blood,

muscle, gut, brain, etc).

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The second category includes so-called intravascular devices for plasmapheresis. There are a number of these patents by Gorsuch and Co-workers. These patents disclose the diffusion of plasma across semi-rigid membranes in highly complex shapes, but do so in order to remove deleterious plasma proteins. They do not

5   specifically address the removal of fluid/water, even though a "byproduct" of the described techniques is removal of the fluid in which the deleterious proteins reside. In fact, in traditional plasmapheresis, there is no desire or intent to remove fluid per se, so that usually, the water volume is intentionally restored by re-infusing sterile fluids. In addition, some complex devices have been designed to remove targeted proteins from the

10   extracorporeal plasma, and then return the rest of the plasma to the patient (as disclosed in Gorsuch 4,950,224 and 5,224,926). Additionally, Gorsuch 5,735,809 states "... the separated plasma may be treated for removing antibodies, antigens, pathogens, toxins and other undesirable materials." In Gorsuch, there is no teaching of merely removing fluid in the treatment of volume-overload states. Gorsuch, in patent 5,980,478, specifically

15   indicates a desire to be able to remove the plasma fluid in its entirety and replace fluids separately as deemed necessary. This is in essence, a "poor man's dialysis," and much is made of the fact that it would preclude the need for purchasing dialysis equipment. Gorsuch refers to this technique as "PUT," as in Plasma Ultrafiltration Therapy. This device still removes plasma with all its constituent proteins (both good and bad), because

20   Gorsuch specifically makes note of a sieving coefficient cutoff of between $2 \times 10^4$ and $4 \times 10^6$ Daltons. The reason for this is that this method utilizes the older Gorsuch

plasmapheresis technology. This presents a problem because the method is not safe for patients since the high volumes of ultrafiltrate will contain many important and beneficial proteins, and the patient may be seriously jeopardized if the fluid is continuously discarded.

5        The third category includes patents directed to intravascular hemodialysis devices, such as 4,235,231; 5,968,004; and 5,980,478. Patent 5,902,336 is directed not to an intravascular device, but rather to a device surgically connected to a blood vessel and drains directly into the patient's own bladder for fluid removal.

         The fourth category includes patent numbers 4,563,170; 5,360,397;

10    6,030,358; 6,238,366; and 6,234,991. The '170 and '397 patents are not relevant since they are extracorporeal in nature and are variations on traditional blood purification devices such as hemodialysis. The '358 patent is not relevant since it discloses a microcatheter to deliver a therapeutic agent into a tissue. The '366 patent is not relevant since it is an extracorporeal fluid management device to help nursing staff keep track of

15    input/output so as to balance fluid administration. Finally, the '991 patent is not relevant because it describes a method of enhancing peritoneal dialysis clearances.

Brief Summary of the Invention:

         The invention provides, in one aspect thereof, an intravascular device for removing plasma from a patient's whole blood. The device is a sealed dual lumen

20    catheter, i.e., a catheter comprising at least two channels, preferably in coaxial

configuration, and allowing fluid entry into one channel and fluid egress, or exit via a direct connection to the other channel. The device is placed within a patient's blood vessel, and plasma from the patient's blood is driven through the catheter wall into the device by osmotic forces created by a hyperosmotic fluid which is continuously supplied

5      through said lumens. The device is so constructed as to enable whole blood to come into contact with a semipermeable, hydrophilic membrane such as preferably, a hydrophilic polyamide, a modified polytetrafluoroethylene, i.e., one similar to Teflon ® or a polyether sulfone forming the outer surface of the body of the catheter, whereby the plasma fluid portion thereof passes through the membrane due to the osmotic pressure

10     exerted by a hyperosmotic fluid, preferably dextrose, but also including larger sugars such as disaccharides, oligosaccharides, starches, and low molecular weight dextrans flowing along its inner surface within a lumen of said device. Fresh hyperosmotic fluid is continuously supplied by the second lumen of the dual lumen device. Thus, the plasma fluid is removed from whole blood, *in vivo*. The invention also provides a method of

15     removing plasma fluid from whole blood by utilizing the device, which is inserted into a patient's blood vessel.

The invention also overcomes some of the shortcomings of known extracorporeal methods by separating plasma fluid from the particulate blood components (i.e. red blood cells, white blood cells, platelets) intracorporeally, by using the device

20     within a blood vessel. Thus osmotic pressure is utilized instead of the negative hydraulic pressure induced by pumped methods as described in the prior art.

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Brief Description of the Several Views of the Drawings

Figure 1 is an external plan view of the device;

Figure 2 is a longitudinal cross sectional view of the device;

Figure 3 is a transverse cross-sectional view of the device along line a – a' of Figure 2; and

Figure 4 is a further view of the device of Figure 2 showing additional elements of the device;

Figure 5 is an external plan view of a different embodiment of the device; and

Figure 6 is a transverse cross-sectional view of the device along the line b – b' of Figure 5.

Detailed Description of the Invention:

The primary therapeutic goal of the method of the invention performed using the device is removal of fluid volume, rather than the small amounts of solutes or toxins that are cleared by the convection of bulk liquid. The osmotic gradient or pressure required to induce the necessary rate of fluid removal will depend on the permeability of the device's wall (i.e. ultrafiltration coefficient) and its surface area. Increasing the porosity of the semipermeable barrier not only increases fluid loss, but also reduces its effective sieving and thereby allows convective losses of larger solutes or toxins. Intra-device collapse and flow irregularities are avoided in the present invention by using osmotic gradients, which distend the internal lumens. This is an important conceptual

difference between the effects of prior art pump-driven hydraulic pressure gradients and osmotic gradients. Although the ultrafiltration coefficient of the semipermeable membrane suggests that there would be equal fluid losses for comparable pressure gradients, the device would not perform as well nor be as long-lived if it were vacuum-driven.

The semipermeable membrane used in the invention is formed, preferably of a highly biocompatible and hydrophilic material, having a high ultrafiltration coefficient and a molecular weight cut-off below that of the osmotic agent, i.e., 180 Daltons in the case of dextrose. There are a number of permutations and variations in the types of membranes that may be devised to achieve the desired goal. In a preferred embodiment, the membrane is a polymeric flexible membrane. Among these are a) hydrophilic polyamides; b) hydrophobic fluorocarbons, such as the hydrophobic polytetrafluororethylene (PTFE) [Dupont's Teflon®] modified to make them more hydrophilic (such as with charged molecules as in Dupont's Nafion®; c) polyether sulfone; d) siloxanes or polysiloxanes; or e) polysulfones. Another approach to the problem is to impose size selectivity of the membrane with a thin layer of a tight polymeric membrane, (such as a polysulfone) and to maintain the structural integrity of the membrane with a separate and highly porous skeleton layer (such as a polysulfone or a polyurethane). Such dual layered membranes are typically made by a process of co-extrusion of the polymers; or a process in which one of the polymers is sprayed as a layer on top of the underlying polymer, which is the support structure.

The feasibility of applying the concept for human use is demonstrated by calculating predicted osmotic losses. Typical patient applications medically necessitate removing 2-3 ml of plasma fluid/minute, for a total of up to about 3- 4 liters/day. Polymer or silicone-based membranes can be formed by extruding them in the shape of catheters or flat sheets that are turned into tubes by means of a seam, and can easily have ultrafiltration coefficients ranging from single digit amounts to as much as 50 ml/hour/m$^2$ membrane/mm Hg transmembrane pressure. As a practical example, one can utilize a membrane with an ultrafiltration coefficient of 10 ml/hour/m$^2$/mm Hg gradient in order to remove 3 ml/min (180 ml/hour). An intravenous catheter, such as those placed in the inferior vena cava by way of the femoral vein, can have surface areas in the range of 20 cm$^2$. One can then calculate the necessary pressure gradient to produce this goal of 180 ml/hour using a 0.002 m$^2$ device with a coefficient of 10 ml/hour/m$^2$/mm Hg pressure. This yields a value of 9000 mm Hg. One can convert that pressure gradient from mm Hg to the equivalent milliosmole gradient by dividing by the 19.33 conversion factor, yielding 466 milliosmoles/kg water. Since human whole blood has an osmolality of approximately 300 milliosmoles/kg and since non-ideal conditions are often considered to have only about 93% efficiency, the device's lumen would need to have an osmolality of approximately 824 milliosmoles/kg. That osmolality could easily be provided by fluids currently commercially available and typically in use for other applications in a hospital setting, such as sterile 20% dextrose solutions. The gradient is maintained by optimizing the flow rate for supplying fresh solution.

As pointed out above, fluid removal is most effective when it is osmotically driven across the device's external surface comprising a semipermeable membrane or barrier, and into a lumen of the catheter. In a simple embodiment of this concept, the device is a dual lumen catheter of coaxial configuration, and the two lumina

5    (the inner and the outer lumina) are connected at the distal end of the catheter. (In another embodiment, the device is a dual lumen catheter of side-by-side configuration.) A high osmolality fluid (such as a sterile dextrose solution) flows into the inner lumen to the distal end of the catheter, reverses direction and thus flows back out of the catheter through the outer lumen. The high osmolality fluid is therefore flowing past the inner

10   surface of the semipermeable membrane of the outer catheter wall. In a simple application of this example, the sterile catheter is inserted percutaneously using a sheath or guide wire into a blood vessel, ideally a large vein such as the internal jugular or femoral vein. The use of a sheath has the additional advantage of protecting the potentially fragile outer surface of the catheter during its insertion. The catheter is then

15   anchored in place using skin sutures into a retaining attachment (i.e. plastic wings). The port leading to the inner lumen is then attached to a conventional mechanized pump (not shown), which delivers the sterile hyperosmolar fluid. The fluid flows to the distal tip within the inner lumen and then flows back in the outer lumen to the exit port. In other, less preferred embodiments the device is constructed alternative configurations for

20   supplying fresh hyperosmotic fluid to the inner surface of the semipermeable catheter wall. These include various dual lumen catheters with side-by-side or eccentric channels

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rather than the preferred coaxial configuration.

In use, it is intended that the device be placed in the lumen of a blood vessel. Veins are preferable to arteries in order to minimize bleeding at the entry site. Although the device can be inserted into the blood vessel, which is under direct

5      observation during an open minor surgical procedure (referred to as a "cut-down"), the preferred and less complicated method is to place it percutaneously. The technique is currently considered a standard practice, and is summarized as follows: Typically, the vein is identified by physical exam or by ultrasonic guidance. The skin covering the vein is prepped by cleaning it with a sterilizing solution. The sterilized field is protected by

10     surrounding it with sterile surgical drapes. Local anesthesia is effected by subcutaneously injecting an anesthetizing medication. A small needle is used to enter the vein, allowing the threading of a guide wire into the vessel. The needle is removed by sliding it off the guide wire, leaving just the wire in place. A flexible, dilating breakaway sheath is slid over the wire and gently pushed into the vein using a twisting motion, thereby using its

15     conical tip to enlarge the hole in the vessel. The guide wire is then removed, leaving the sheath in place. With the stiff wire within the central channel, the ultrafiltration device is slid through the sheath into the blood vessel. The sheath is gently pulled out of the vessel, and discarded by pulling apart its breakaway sides. The ultrafiltration device is then secured to the skin using sutures and, optionally, a wing-like anchor. The stiff wire

20     is then removed. The inlet and outlet tubing ports are then connected to the apparatus supplying and draining the osmotic ultrafiltration fluid. In this configuration, blood

remains on the outside of the catheter's semipermeable wall, and the high osmolality fluid

traverses its inner surface. Plasma fluid is thereby osmotically driven across the catheter

wall into the fluid compartment and exits via the exit port.

Referring now to the drawings, Figures 1-4 illustrate an embodiment of the device

5    wherein the two lumina are coaxially configured. Specifically, Figure 1 shows in plan

view, the catheter of the invention, having outer surface 6 of the main body of the device

and which corresponds to the circumferential (outer) lumen of the device, inlet port 1 and

outlet port 4, each having attached to the end thereof, luer locking devices 2 and 5

respectively, for connecting inlet port 1 to an external (not shown) source or supply depot

10    for fresh hyperosmotic fluid, and for connecting outlet port 4 to an apparatus (not shown)

for draining and collecting used hyperosmotic fluid. Luer lock connector 5 may optionally

be fitted with the hub 3 of the stiff wire 12 (described below) used to enhance the

stiffness or rigidity of the device during placement thereof. Figure 2 is a more detailed

view in longitudinal cross-section of the device illustrated in Figure 1. As shown in this

15    drawing figure, central, or inner lumen 7, having wall 8 of nonpermeable polymer is

coaxially disposed within the circumferential or outer lumen. Arrows 9 and 10 show the

direction of flow of hyperosmotic fluid into and out of the device respectively. More

particularly, fluid entering the inlet port 1 flows, as shown by arrow 9 along the length of

the inner lumen until it reaches the open, distal end thereof and reverses direction as

20    shown by arrow 10 and ultimately exits the device through outlet port 4 after having

removed blood plasma from whole blood during its traverse of the device. Figure 3, a

cross-sectional view along line a-a' of Figure 2 is provided to illustrate the septum 11

provided between the two lumens to maintain the structural integrity of the device and the

integrity of the coaxial geometry of the lumens. Figure 4 illustrates the stiff wire 12

connected to hub 3 (mentioned above) which may be placed within the central or inner

5        lumen to enhance and maintain the stiffness of the device during its placement in a blood

vessel. Additionally as shown in Figure 4, there is optionally provided an anchor 13 for

holding the device securely in place on the surface of a patient's skin while it is in use.

Anchor 13, if provided, is provided with holes 14 to enable the anchor to be sutured or

otherwise affixed to the patient's skin.

         Figures 5 and 6 illustrate an alternative embodiment of the catheter device

wherein the 2 lumens are disposed in a side-by-side configuration, rather than the coaxial

configuration shown in Figures 1 through 4.

         Figure 5 is an external view of the dual lumen catheter arranged in a side-

by-side configuration. Like numbering is used to identify elements common to both

15       configurations. Thus, as seen in Figure 5, the device is provided with an external surface

8 formed of a semipermeable membrane. The device is provided with inlet port 1 leading

to inflow channel 7, corresponding to inner lumen 7, and outlet port 4 connected to

outflow channel 11. Luer locks 2 and 5, the latter being optionally provided with hub 3

of stiff wire 12. Wings 13 provided with holes 14 to secure the device to the patient's

20       skin are also provided; and finally, as shown in Figure 6, which is a transverse cross-

sectional view of the embodiment of Figure 5 illustrates septum 11 provided between the

side-by-side lumens to separate them and maintain the structural integrity of the device. Distal end 15 of the catheter is where the inflow 7 and outflow 11 channels or lumens connect.

Coating, caking or clotting on the outside of the catheter is minimized by using a biocompatible material, a small diameter and a pump system which avoids negative hydraulic pressure across and thereby collapsing the wall. The catheter specifications (i.e. length, diameter) and the pump speed are determined by the osmolality of the solution (i.e. 10, 20, or 50% dextrose solutions), the permeability of the outer wall, and are interrelated to achieve the desired ultrafiltration rates.

In a typical application the catheter would be in continuous use and provide slow ultrafiltration for many days. For example, dextrose concentration and pump speed would be set to achieve ultrafiltration of 1 - 3 ml/min and thereby total about 2 - 4 liters of fluid removal/day. In embodiments designed for the purpose of effecting highly regulated and controlled fluid removal, the basal pump rate of the hyperosmolar fluid as well as the ultrafiltration rate are achieved using mechanical pumps. In one example, the basal rate of fresh fluid is delivered by a precise inflow pump, and the desired ultrafiltration rate is added to that basal rate to determine the rate of the independent pump on the outflow circuit (i.e. 100 ml/min of 20% dextrose pumped inflow and 102 ml/min pumped outflow to achieve ultrafiltration of 2 ml/min). The parameters of such user-defined pump speeds must be restricted so as to prevent setting an ultrafiltration rate in excess of that produced by the osmotic fluid losses; otherwise there will result a

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hydraulic convective fluid component to the fluid removal. As indicated above, this

vacuum-induced negative hydraulic pressures may cause the catheter to collapse and

induce regions of erratically high and low flows across the membrane, thereby causing

the system to fail prematurely, as a result of caking of protein or other particulate matter

5    (i.e. fibrin, platelets, or red blood cells).


A number of pumping systems can be used to accomplish this so-called

highly regulated fluid removal. As described above, separate inflow and outflow pumps

can be utilized. In another embodiment, pumps (i.e. rotating peristaltic or occlusion

pumps) or balancing chambers can be utilized to equalize the inflow and outflow rates.

10    Fluid removal can then be accomplished by a separate, highly calibrated pump on the

outflow portion of the circuit, placed between the catheter and the equalizing pumps. An

alternative pumping system would result in certain advantages such as potential

miniaturization, and cost-containment by utilizing a recirculating reservoir of high

osmolality solution. For example, if a 10% dextrose solution is otherwise effective, one

15    could instead use a 50% dextrose supplied in an underfilled bag serving as the reservoir

for the recirculating luminal fluid. Continuous weighing of the reservoir bag would

enable one to monitor the fluid removal and serve as a fail safe mechanism in addition to

setting the pump rates as mentioned above. In still another embodiment, there could be a

single pump from the reservoir into the catheter's inner lumen and the rate of that pump

20    would be regulated by a feedback mechanism based on the rate of fluid accumulating in

the weighed reservoir. Since these reservoir embodiments would be self-contained systems lasting many hours, they would also have advantages from a cost and nursing labor point of view. Overall, and regardless of the exact pumping configuration, the device and pumps would have a very high safety profile because of the long history of successful design and use of dual lumen catheters, and because the flow paths are connected to sealed sterile systems. In the event that a leak occurs, it would still be extremely safe because of the use of sterile solutions, i.e. sugar solutions. Safety can be further improved by placing a blood leak detector on the outflow track (e.g. tubing placed on an external optical sensor set to the proper wavelength to detect the presence of hemoglobin). Catheter longevity can be optimized by the choice of the biocompatible material, such as a synthetic polymer or silicone derivative. Longevity may be further enhanced by intermittently providing positive internal pressure and causing momentary hydraulic outflow from the lumen across the wall and into the blood vessel. The transient reversal of the flow direction would serve to debride or clean the catheter surface. This could be accomplished by many mechanical means, including momentary restriction of the outflow track or altering the relative pump speeds.

Notably, the composition of the semipermeable catheter membrane is selected depending on the sieving characteristics desired to produce the ultrafiltrate. For example, in the simplest embodiment designed to treat congestive heart failure (fluid overload), the wall characteristics are those which are calculated to remove just plasma

water with limited removal of small sized electrolytes (such as sodium, potassium, chloride, bicarbonate or small toxins) but lacking pores large enough to remove plasma proteins (i.e. albumin, immunoglobulins). In still another embodiment, the pores can be selected to be much larger and thereby allow removal of larger substances, such as

5      proteins, similar to plasmapheresis. However, as indicated above the flow rates would typically be so low as to limit the total daily mass clearance of these larger moieties.